PATHOLOGICAL PHYSIOLOGY AND GENERAL PATHOLOGY

Adrenergic Regulation of Interleukin Production by Bone Marrow Cells under Conditions of Immobilization Stress

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Among the hemopoietic growth factors, interleukins 1 and 3 play a crucial role in the synergic regulation of the proliferation and differentiation of polypotent and committed hemopoietic precursors [11]. On the other hand, the production of these cytokines is greatly stepped up when urgent stimulation of hemopoiesis is required [9], for example, during stress [2,4], which is known to be accompanied by activation of the sympathetic-adrenal system [8]. In the opinion of many scientists, catecholamines can, via the β-adrenoreceptors, stimulate [13] or suppress [12] interleukin-1 (IL-1) production by macrophagal cells. At the same time, data on adrenergic regulation of interleukin-3 (IL-3) secretion are almost entirely lacking.

In this connection, the aim of our investigation was to study the role of the adrenergic structures in the regulation of cytokine production during immobilization stress.

MATERIALS AND METHODS

The experiments were carried out in the fall-winter season in the morning hours on 180 male F_1 (CBA×C57Bl/6) mice weighing 18-20 g (Rassvet, Tomsk). The animals were bound softly in the supine position for 10 h. The α-adrenoblocker dihydroergotamine (3.9 mg/kg) or the β-adrenolytic propranolol (5 mg/kg) were twice injected subcutaneously, 3-5 min prior to and 5 h after the start of immobilization. The stressed control mice were administered an equal volume of physiological saline (0.2 ml). The animals were sacrificed by cervical dislocation at diverse times (1-8 days) following the treatment. The level of IL-1 and IL-3 activity was biologically tested in the bone marrow cell supernatants [5]. The level of activity was measured in arbitrary laboratory units (a.l.u.). The logarithm of supernatant dilution, for which the incorporation of ^{3}H-thymidine in the target cells increased twofold, was taken as a unit of activity. The data were statistically processed using Student's test and Wilcoxon's rank T test [6].

RESULTS

It was established in our experiments that on days 2 and 5 a 10-h immobilization of F_1 (CBA× ×C57Bl/6) hybrid mice resulted in a statistically significant elevation (to 254-270% of the initial level, respectively) of IL-1 activity in the supernatants of lipopolysaccharide (LPS)-stimulated adhesive myelokaryocytes (Fig. 1). In turn, an increased IL-3 production (judged by an increase of its activity) by Con A-stimulated nonadhesive bone

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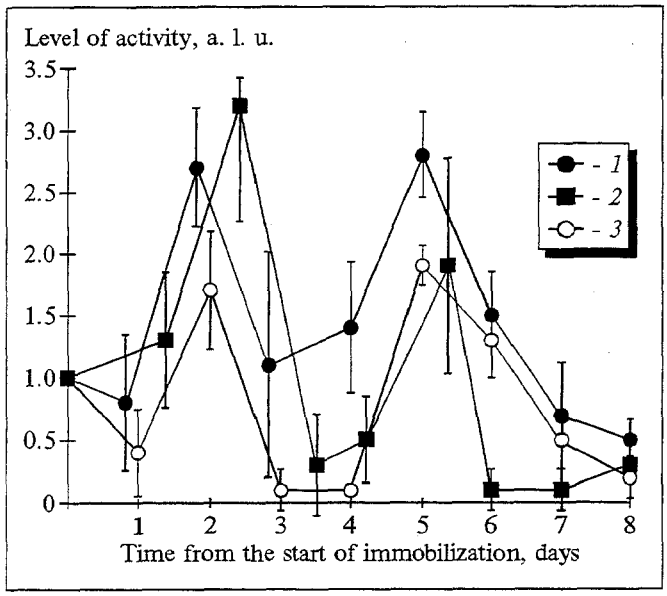

Fig. 1. Time course of IL-1 activity in supernatants of LPS-stimulated adhesive myelokaryocytes for administration of pharmacological adrenergic antagonists to F_1 (CBA×C57Bl/6) mice subjected to a 10-h immobilization. Here and in Fig. 2: *1*) physiological saline; *2*) α-adrenoblocker; *3*) β-adrenoblocker. Confidence intervals shown for $p=0.05$.

marrow nuclears was noted on days 1-2, 4-5, and 7 from the start of exposure, the maximum activity (395% of the initial value) being attained by the 4th day (Fig. 2). The production and biological significance of these cytokines are known to increase markedly in emergency situations [9], including immobilization stress [4].

Administration of the pharmacological antagonist of a-adrenergic structures to immobilized mice caused a prolonged reduction of IL-1 production by the bone marrow nuclears, which was most pronounced on days 3-5. Worthy of note was a reliable inhibitory effect of α-adrenoblocker (1.4-fold) on the stress-induced enhanced production of the monokine on day 5. On the other hand, the β-adrenergic antagonist virtually did not produce any marked effect on the dynamics of IL-1 activity in the conditioning media (Fig. 1). The use of Wilcoxon's rank T test confirmed the presence of a suppressive effect in the case of α-adrenoblocker ($\alpha_T<0.01$) and its absence in the case of β-adrenoblocker ($\alpha_T<0.05$). To a certain extent our findings concur with the view that an elevated cAMP level in the macrophages exerts a suppressive effect on their IL-1 production [12], since pharmacological blocking of the α-adrenoreceptors alters the ratio between the intracellular cyclic nucleotides in favor of adenosine monophosphate [7].

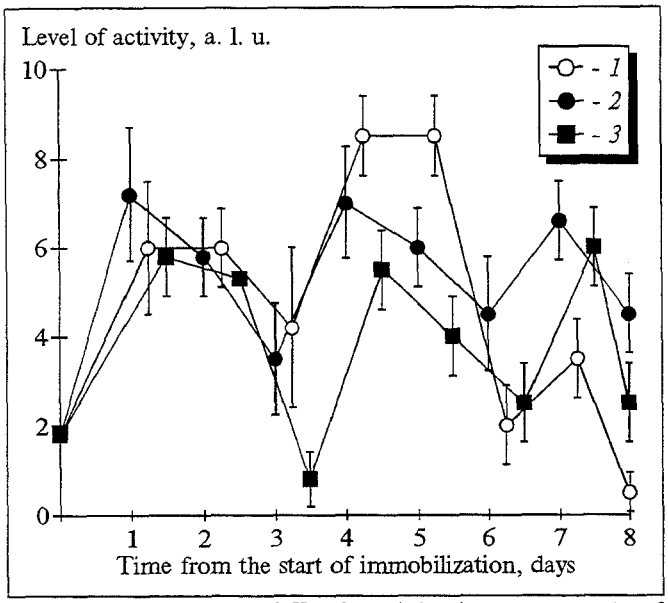

Fig. 2. Time course of IL-3 activity in supernatants of ConA-stimulated adhesive myelokaryocytes for administration of pharmacological adrenergic antagonists to F_1 (CBA×C57Bl/6) mice subjected to a 10-h immobilization.

Pharmacological adrenergic antagonists had a pronounced modulating effect on the dynamics of IL-3 activity for ConA-stimulated nonadhesive bone marrow nuclears (Fig. 2). Specifically, administration of β-adrenoblocker to stressed mice reliably reduced the lymphokine content in the supernatants on the 3rd day (below the initial level), and, more interestingly, on the 5th day of the experiment (practically, 1.5-fold as compared to the stressed controls). Injection of α-adrenoblocker suppressed the ability of nonadhesive myelokaryocytes to produce IL-3 on days 7-8. However, on the 5th day the level of IL-3 activity in immobilized animals receiving α-adrenoblocker was 134% higher than that in the stressed mice given physiological saline alone. The Wilcoxon rank T test was indicative of an inhibitory effect of β-adrenoblocker on IL-3 production ($\alpha_T<0.01$) and of its absence in the case of α-adrenergic antagonist ($\alpha_T>0.05$). The marked differences in the dynamics of IL-3 activity in the stressed mice given α- or β-adrenoblocker may be due to nonuniform changes in the intracellular concentrations of secondary messengers in the lymphokine-producing T cells. In addition, a change of subpopulations of the hemopoiesis-regulating T lymphocytes, which are known to exhibit diverse density and functional activity of the adrenergic receptors [1], has been shown to occur in the bone marrow in response to immobilization [10].

Thus, there is no doubt that the adrenergic structures actively contribute to regulation of IL-1 or IL-3 production by the cells which form the hemopoiesis-inducing microenvironment (HIM) throughout the time course of the stress response of the hemopoietic tissue. The desynchronization of cytokine production by adrenoblockers leads to the

conclusion that, during stress, catecholamines are evidently important for the formation of a definite rhythm of concerted production of cytokines, which is responsible for enhanced growth of early hemopoietic precursors [11]. On the other hand, the active metabolism of adrenergic antagonists [3] is evidence that it is precisely at the early stages of development of the immobilization-induced stress response that the interaction between the sympathetic nervous system and the cells of HIM plays an important role in the enhanced production of cytokines.

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Adaptation to Periodic Hypoxia Restricts Subdural Hemorrhage during Audiogenic Epileptic Seizures in Rats

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Adaptation to periodic hypoxia in a pressure chamber exhibits various protective effects in experiment and clinical practice [5,6]. In particular, it raises the rat's resistance to audiogenic epileptic seizures and reduces the severity of seizures [1,5]. Until recently, however, it was unclear how preadaptation to hypoxia under the conditions used for treating patients (for example, those with bronchial asthma and neuropsychic diseases) [6] affects the severity of the subdural hemorrhage usually observed in the brain during audiogenic epilepsy in Krushinskii-Molodkina (KM) rats [1]. The importance of this topic stems from the fact that adaptation to periodic hypoxia has not yet been used in the management of epilepsy in clinical practice.

The objective of the present study was to assess the effect of preadaptation to prolonged periodic hypoxia under clinically approved conditions

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